PROPYLENE GLYCOL
Livestock

Executive Summary

Propylene glycol is a 3-carbon compound derived from propylene which has applications in both industry and medicine. The subject of the current petition is a request for the approval of propylene glycol to the National List for medical use in organic livestock. Propylene glycol is used as a drench in the treatment of ketosis. Propylene glycol is considered GRAS, except when used in or on cat food.

Summary of TAP Reviewers' Analyses[1]

Synthetic/ Nonsynthetic	***Allow without restrictions?***	***Allow only with restrictions? (See Reviewers' comments for restrictions)***
Synthetic (3)	Yes (1) No (2)	Yes (2) No (1)

Identification

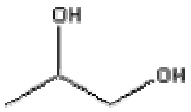
Chemical names: 1,2-propanediol; 1,2-dihdroxypropane; Methyl glycol; Methylethylene glycol; Trimethyl glycol, $C_3H_8O_2$; $CH_3CHOHCH_2OH$

Other Names: 1,2-propylene glycol; 2-hydroxypropanol; *alpha*-Propylene glycol; *alpha*-propyleneglycol; Colla-Moist WS; Dowfrost; Horsechestnut HS; Methylethyl glycol; Methylethylene glycol; Monopropylene glycol; PG 12; Propane-1,2-diol; Propylene glycol; Propylene glycol USP; Sentry Propylene glycol; Sirlene; Solar winter ban; Uantox 20; Uantox 3; 1,2-proylenglykol [German]

CAS Number: 57-55-6

Other numbers:
EPA Pesticide Chemical Code: 068603

Chemical Structure:



[1] *This Technical Advisory Panel (TAP) review is based on the information available as of the date of this review. This review addresses the requirements of the Organic Foods Production Act to the best of the investigator's ability, and has been reviewed by experts on the TAP. The substance is evaluated against the criteria found in section 2119(M) of the OFPA [7 USC 6517(m)]. The information and advice presented to the NOSB is based on the technical evaluation against that criteria, and does not incorporate commercial availability, socio-economic impact, or other factors that the NOSB and the USDA may want to consider in making decisions.*

Characterization

Composition:

Propylene glycol ($C_3H_8O_2$) is a 3-carbon compound derived from propylene. It contains two hydroxyl (OH-) groups, located on carbons 1 and 2. Propylene glycol is manufactured by treating propylene with chlorinated water to form the chlorohydrin, which is then converted to the glycol by treatment with sodium carbonate solution. Propylene glycol is also prepared by heating glycerol with sodium hydroxide and distilling the mixture.

Properties:

Appearance: Thick, clear, oily liquid.
Odor: Odorless.
Taste: Tasteless.
Solubility: Miscible in water.
Specific Gravity: 1.035-1.037 at 25°C
Boiling Point: 188.2°C (370°F)
Melting Point: -59°C (-74°F)
Vapor Density (Air=1): 2.6
Vapor Pressure (mm Hg): 0.129 at 25°C (77°F)
Evaporation Rate (BuAc=1): 0.01
Stability: Stable under ordinary conditions of use and storage.[2]
Degradation: In air, half will break down within 24-50 hours. In water and soil, it will break down within several days to a week.[3]
Hazardous Decomposition Products: Carbon dioxide and carbon monoxide may form when heated to decomposition. Aldehydes or lactic, pyruvic, or acetic acids may also be formed.
Hazardous Polymerization: Will not occur.
Incompatibilities: Strong oxidizing agents.
Conditions to Avoid: Heat, flames, ignition sources and incompatibles.[4]

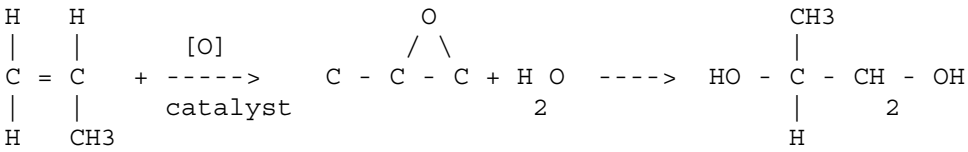
How Made:

Glycols are a class of compounds characterized by two hydroxyl (OH-) groups on separate carbons of an organic structure, usually linear and aliphatic. The most common subclassification of glycols is the 1,2-diols, in which propylene glycol is one of the most important members. Generally, 1,2-diols may be produced by hydrolysis of epoxides, chlorohydrins, or 1,2-dichlorides, or by catalytic reduction of α-keto- or α-hydroxyaldehydes or ketones. 1,2-propylene glycol (1,2-propanediol) is produced by the reaction of propylene oxide with water.[5]

Propylene, also known as propene, is an unsaturated hydrocarbon. It is an important petrochemical feedstock. It is obtained as a by-product of gasoline manufacture by the fluid cracking of gas oils, or from ethylene in the steam cracking of hydrocarbons, in which a mixture of steam and hydrocarbon is passed through a tube heated to 600-900°C (1110-1650°F). About 10% of the propylene that is manufactured is converted into propylene oxide, C_3H_60, either by a reaction with hypochlorous acid, HOCl, followed by calcium hydroxide, or in a one-step reaction with hydroperoxide, ROOH, in the presence of a molybdenum or vanadium catalyst. Propylene oxide is then hydrolyzed to propylene glycol or polymerized to polypropylene glycol, or used in the preparation of polyurethanes, detergents, hydraulic fluids, etc.[6]

---

[2] "Material Safety Data Sheet: Propylene Glycol." Mallinckrodt Chemicals. http://www.mallchem.com/msds/p6928.htm 2 November 2001.
[3] "ToxFAQs ™ for Ethylene Glycol and Propylene Glycol." Agency For Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/tfacts96.html September 1997.
[4] [See [2]]
[5] McGraw-Hill Encyclopedia of Science & Technology. vol. 8. McGraw-Hill, Inc, 1992. pp. 145.
[6] McGraw-Hill Encyclopedia of Science & Technology. vol. 14. McGraw-Hill, Inc, 1992. pp.429.



The following is a research summary regarding the use of microbial catalysis to form propylene glycol from sugars. The goal of this research is to find more environmentally-friendly manufacturing alternatives. The second text is an excerpt from another report regarding the use of sorbitol as the sugar from which to generate propylene glycol.

Microbial Catalysis for the Conversion of Sugars and Other Renewable Materials to Propanediols:

D. C. Cameron, University of Wisconsin-Madison. (References: Cameron 1995a, b, c, d; Skraly 1994)

Goal:
The overall goal of this project is to develop environmentally friendly processes for the production of chemicals from renewable feedstocks using microbial catalysis. The specific goal is to develop microbial catalysts for the production of propanediols that will lead to processes with advantages over current chemical processes.

Rationale:
The on-going work addresses the microbial production of 1,3-propanediol (1,3-PD) and 1,2-propanediol (1,2-PD, also known as propylene glycol). 1,3-PD is currently a relatively small volume specialty chemical. However, it has the potential to be a large-volume commodity chemical for the production of polymers used in carpet fibers and other products, and was recently called a potential "blockbuster" (C&EN, July 17, 1995, p. 11). 1,2-PD is currently a large volume commodity chemical, with over 950 million pounds produced in the U.S. in 1994 and a 13% annual growth (C&EN, June 26, 1995, p. 40). 1,2-PD is used in unsaturated polyester resins, human and animal foods and as a non-toxic replacement for ethylene glycol in automobile antifreeze and airplane wing deicing fluids.

Both 1,3-PD and 1,2-PD are currently produced by synthetic processes starting with petrochemical feedstocks. Chlorinated intermediates are used in their production. Microbial catalysis provides routes to both 1,3-PD and 1,2-PD from renewable feedstocks without the use of or generation of chlorinated intermediates. Furthermore, in the case of 1,2-PD, the current synthetic route gives a racemic mixture, whereas, microbial catalysis gives a pure stereoisomer. As described above, both 1,3-PD and 1,2-PD are attractive target chemicals for microbial production. The initial CenCITT funding supported work on 1,3-PD and exploratory work on 1,2-PD. Due to funding limitations, CenCITT is currently only supporting work on 1,3-PD. Limiting the work to 1,3-PD at this time is reasonable, since 1,3-PD is at an earlier phase in its commercial development than 1,2-PD, so research and development of new processes will have a greater initial impact. The 1,2-PD work, however, also has much promise; in fact, work on the production of this chemical from lactose is currently being funded by the Center for Dairy Research at the University of Wisconsin-Madison. In addition, an Environmental Protection Agency/National Science Foundation proposal on 1,2-PD production was recently selected for funding starting in October 1995.

Approach:
Several existing species of microorganisms are able to produce 1,3-PD by the fermentation of glycerol. Glycerol is a relatively expensive feedstock. Sugar, however, is inexpensive (less than $0.10/lb), and should become even less expensive as processes for the hydrolysis of biomass to sugars are developed. Therefore, the specific objective of this project is to develop new microorganisms with the ability to convert sugars directly to 1,3-PD. Three basic approaches are under investigation: 1) adding the ability to convert "sugars to glycerol" to an organism that is naturally able to convert "glycerol to 1,3-PD", 2) adding the ability to convert "glycerol to 1,3-PD" to an organism that is naturally able to convert "sugars to glycerol", and 3) adding both sets of abilities to an organism that naturally has neither. Adding the "sugars to glycerol" pathway involves adding one or two new genes to the existing

glycolytic pathway. Adding the "glycerol to 1,3-PD pathway" involves adding genes for glycerol dehydratase and 1,3-propanediol reductase.

Status:
The key enzyme for the conversion of sugars to glycerol is glycerol phosphatase. This enzyme has been purified from Bacillus licheniformis, a glycerol producing bacterium. The enzyme was found to have a unique activity, in that it is specific for D-glycerol-1-phosphate (DGP). All other known glycerol phosphatases are specific for L-glycerol-1-phosphate (LGP), or have roughly the same activity for both substrates. The discovery of a D-glycerol phosphatase is significant in that it provides a means to decouple metabolic reactions involved in growth from reactions involved in energy production. LGP is involved in the production of cell membranes needed for cell growth. A pathway that uses DGP for glycerol production (an energy generating reaction) will not compete with membrane formation. Work is currently underway to clone and sequence the gene for the D-glycerol phosphatase. Work is also underway to find the enzyme responsible for DGP formation. Such an enzyme is needed to complete the novel "sugar to glycerol" pathway. It should be noted that the discovery of the D-glycerol phosphatase also provides a novel route to LGP involving the kinetic resolution of racemic glycerol phosphate. LGP is an important starting material for synthetic phospholipids. It should also be noted that glycerol itself is an important chemical, and that the enzyme will be useful in developing improved glycerol-producing organism. The genes involved in the conversion of glycerol to 1,3-PD have been cloned, sequenced, and expressed in E. coli. Work is currently underway to express these genes in a natural glycerol producer, such as yeast or Bacillus licheniformis. Several genetic constructs have been developed and a variety of transformation methods have been investigated. The work is progressing well, and no major obstacles to progress are envisioned. [7]

Glycols from Sugar

…Reactor Data

Sorbitol can be cracked in the presence of hydrogen to yield a variety of different oxygenated products including ethylene glycol, propylene glycol, glycerol, and lactic acid. Also produced are various alcohols, C4/C5/C6 diols, and triols. The reaction is catalyzed by a ruthenium catalyst at a pressure in excess of 1500 psig and at temperatures in the 400-500ºF range. Selectivity and conversion data as well as reactor sizing information is provided in the attached patent (US 5403805, April 4, 1995, Ruthenium-Based Catalyst for Producing Lower Polyhydric Alcohols).

The sorbitol must be diluted to a 40 wt% solution. The reaction requires a basic environment and caustic (NaOH) must be added to a 1:3 molar ratio with the sorbitol. Excess hydrogen is required at a level of 20% above that needed for the reaction. The expected catalyst run length is one year before the catalyst must be regenerated by burning off coke formed during the reaction. The catalyst must be replaced every three years.

Purification Section Data

There are three key purification issues for this project:

1. Removal of the Sodium required for the reactor.
Usually, getting the sodium out as soon as practical is suggested, since sodium can cause fouling (salting) problems in downstream equipment.

2. Energy efficient removal of the water in the sorbitol feed.

[7] Cameron, D.C. "Microbial Catalysis for the Conversion of Sugars and Other Renewable Materials to Propanediols." University of Wisconsin-Madison. 1995.
http://cpas.mtu.edu/cencitt/activity_report/crtall95.html#mccsormp

Water is very expensive to boil up a tower because of its high latent heat (about 1000 BTU/lb). It is important to try and reduce this cost.

3. Purifying the products (sequence of distillation towers).
There are a number of difficult separations due to low relative volatilities and/or azeotropes. These components are also very high boiling point so that the use of vacuum and hot oil/fired furnaces may be required in a number of towers. [8]

Specific Uses:

There are many uses for propylene glycol and only a few are highlighted below:

Propylene glycol is one of the most commonly used humectants—substances that have a high affinity for water and have a stabilizing action on the water content of a material. Propylene glycol is used to maintain moisture within a narrow range in certain food products, such as coconut and marshmallows, as well as in tobacco.[9] It is also used to absorb extra water and maintain moisture in certain medicines and cosmetics, and is a solvent for food colors and flavors.

Propylene glycol is used in antifreeze and de-icing solutions. It is used as a solvent in the paint and plastics industries, and to make polyester compounds. It is used as a substitute for ethylene glycol mono-alkyl ethers in all-purpose cleaners, coatings, inks, nail polish, lacquers, latex paints, and adhesives. It is also used to create artificial smoke or fog used in fire-fighting training and in theatrical productions.[10]

The basis of this petition concerns the use of propylene glycol as a drench for the treatment of ketosis in ruminants. It is administered on a per-cow basis. Ketosis is a common condition in fresh (heavily lactating) cows that are in negative energy balance, for example due to nutrition imbalance or calving problems. Propylene glycol is a glucose precursor that elicits an insulin response and reduces back fat mobilization when administered to pre-fresh cows. It is generally administered as a once-daily oral drench of 10 to 20 ounces per cow for several days prior to freshening. Due to the difficulty with drenching cows orally, there is an interest in adding propylene glycol directly to the pre-fresh diet. Administering propylene glycol, mixed with 6 pounds of concentrate and fed once daily, was found to be almost as effective as the oral drench. Studies have demonstrated that the daily drenching of cows with propylene glycol during early lactation increases plasma glucose, increases insulin concentrations, and improves reproductive status.[11]

Action:

Propylene glycol provides the ruminants precursors for them to create their own glucose. An alternative, albeit temporary fix that acts directly on the blood glucose level is the administering of intravenous dextrose or glucose (which is allowed). Dextrose may be given intravenously every 8-12 hours. Sometimes in refractory ketosis, insulin is given to inhibit hormone sensitive lipase. Hormone sensitive lipase plays a major role in breaking down fat in the adipose tissue and sending it to the liver, the organ responsible for converting the fat into ketones. However, it is rare to administer insulin to bovines.

Propylene glycol is an essential follow-up to a dextrose I.V. in a ketotic animal. A concern with the administration of propylene glycol intravenously, rather than orally, is muscle damage. The organic cosolvents propylene glycol

---

[8] "Glycols from Sugar." http://fenske.che.psu.edu/Faculty/CMaranas/che464/SugarProject.pdf
[9] Van Nostrand's Scientific Encyclopedia. vol. 1. New York: Van Nostrand Reinhold, 1989. pp. 1479.
[10] "ToxFAQs ™ for Ethylene Glycol and Propylene Glycol." Agency For Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/tfacts96.html September 1997.
[11] Shaver, Randy. "Energy for Dairy Cows During the Transition Period." University of Wisconsin. 1999 Colorado State University Dairy Nutritional Conference. http://ansci.colostate.edu/ran/dairy/shaver.htm

and polyethylene glycol 400 (PEG 400) have been shown to differ in their potential to cause muscle damage following I.V. injection. In previous studies, propylene glycol was found to be more myotoxic than PEG 400, with cytosolic calcium playing a role in mediating this damage. In recent studies, the direct effects of these cosolvents were investigated in the sarcoplasmic reticulum (SR), the specialized endoplasmic reticulum membrane in muscle that mobilizes calcium. The passive permeability of isolated SR microsomal vesicles to calcium was not affected by 5.3% and 10.5% (v/v) propylene glycol and PEG 400. At 10.5% (v/v), a concentration of the organic cosolvent that would not be unexpected at the injection site, PEG 400 stimulated calcium uptake by 40% and 140% in longitudinal tubular-derived and terminal cisternal-derived vesicles, respectively, without significantly altering the ATP hydrolytic activity of the calcium pump. The calcium pumping efficiency (Ca^{2+}/ATP coupling ratio) was therefore also enhanced. On the other hand, at 10.5% (v/v), propylene glycol did not significantly alter either calcium uptake or ATPase activity of the pump. Propylene glycol stimulated calcium efflux from only the terminal cisternae vesicles via a pathway indicative of the ryanodine-sensitive calcium channel, as demonstrated by inhibition of PG-induced efflux by millimolar Mg^{2+}. These results are consistent with multiple interactions of cosolvents with proteins in the membrane bilayer, with the distinction that the two cosolvents differentially influence the calcium pump and release channel, particularly at the terminal cisternae, where there is rapid change of calcium level during excitation-contraction coupling. This data provides further evidence for the role of calcium in mediating organic cosolvent-induced muscle damage. In addition, they provide a possible explanation for the myoprotective effect of PEG 400 (compared to propylene glycol) as a result of increased myoplasmic calcium removal and reduced calcium release.[12]

Excerpts from the following studies provide more information on the use of propylene glycol to treat ketosis:

Feed Additives for the Transition Cow

R. R. Grummer, R. D. Shaver, and S. Gunderson
Department of Dairy Science
University of Wisconsin – Madison
Manitowoc County Extension
University of Wisconsin – Extension

Introduction
The transition period discussed in this paper is the period two weeks prepartum through two weeks postpartum. This period is characterized by intake depression prepartum (Bertics et al., 1992) and slow intake ascent postpartum (Kertz et al., 1991). Prepartum intake depression and slow intake ascent postpartum are major risk factors in the etiology of metabolic and digestive disorders, such as milk fever, ketosis, fatty liver, left-displaced abomasum, and ruminal acidosis. Numerous feed additives are targeted to transition cows by nutritionists for prevention of metabolic disorders and improvement of lactation performance. The purpose of this paper is to review the research base behind this practice for some of the common feed additives.

Additives for Ketosis/Fatty Liver
There is a gradual decline in dry matter intake (DMI) starting two weeks prepartum followed by a precipitous drop 3-5 days prepartum (Bertics et al., 1992). Decline of DMI is about 30% over the last week prepartum causing increased liver triglyceride immediately postpartum (Bertics et al., 1992). Numerous feed additives are positioned for the prevention of fatty liver and ketosis.

Bertics et al. (1992) theorized that administration of glucose precursors prepartum to increase blood glucose may elicit an insulin response and reduce fatty acid mobilization from adipose. Propylene glycol (PG) drenched orally once daily (32 oz) starting ten days prepartum until calving increased plasma glucose and insulin prepartum and

[12] A. Chu, G.A. Brazeau . "Solvent-Dependent Influences on Skeletal Muscle Sarcoplasmic Reticulum Calcium Uptake and Release." Thesis Dissertation. *Copyright 1994, 1999 Academic Press, Inc.*pp. 142-148 (doi:10.1006/taap.1994.1058)

reduced total liver lipids and plasma nonesterified free fatty acids (NEFA) immediately postpartum (Studer et al., 1993).

Grummer et al. (1994) compared 0, 10, 20 and 30 oz PG drenched orally once daily for five days in feed-restricted springing heifers. Increasing dose of PG had positive linear effects on plasma glucose and serum insulin concentrations and negative linear effects on plasma NEFA and beta-hydroxy-butyrate (BHBA) concentrations. Quadratic effects of PG on plasma glucose, NEFA and BHBA concentrations were also observed; the 10 oz dose was nearly as effective as the 30 oz dose for reducing lipid mobilization.

Because of the difficulty of drenching cows orally for several days prepartum, there is interest in adding PG directly to the steam-up ration. Christensen et al. (1997) administered 12 oz PG once daily as an oral drench, in 6-7 lb of concentrate, or in a total mixed ration (TMR) for seven days in feed-restricted springing heifers and cows. Administering PG mixed with concentrate was nearly as effective as the oral drench for lowering plasma NEFA concentrations. Administering PG in a TMR was not effective. Whether or not using a larger dose when administering PG in a TMR would improve efficacy cannot be determined from this trial. This, however, would increase the cost of administering PG and it is unlikely that administering PG in several small sub-doses throughout the day (TMR) would be as effective as pulse dosing PG (oral drench or mixed with concentrate).

Use of PG as a ration additive for early lactation cows has been shown to reduce milk ketones (Fisher et al., 1973) and plasma NEFA and BHBA (Sauer et al., 1973). It does not appear that PG limits concentrate consumption for concentrates containing up to 10% PG (Christensen et al., 1997; Fisher et al., 1973). This suggests that use of PG as a ration additive at 10-20 oz per cow per day for early lactation cows should not depress feed intake as inclusion rates would range from 3-6% and 1.5-3.0% (DM basis) for concentrate and TMR, respectively… [13]

Combinations:

Propylene glycol is used in combination with many other substances. This report focuses on examples of propylene glycol in food and veterinary drug applications.

Status

Historic Use by Organic Farmers:

Drenching with propylene glycol as a solution to ketosis has been used widely with not only bovines, but other livestock such as goats. It is administered as a cure and also as a prophylaxis. Propylene glycol is widely available commercially for these purposes.

USDA, FDA Final Rule:

FDA: The Food and Drug Administration (FDA) classified propylene glycol as "generally recognized as safe," which means that it is acceptable for use in flavorings, drugs, and cosmetics, and as a direct food additive. However, it later stated that it is not GRAS for use in or on cat food.

Following are pertinent excerpts from the **USDA** Federal Organic Foods Production Act of 1990, stating criteria for organic animal production in general and in the area of healthcare, and the revised FDA Code of Federal Regulations, Title 21 – Food and Drugs (April 1, 2001) pertaining specifically to propylene glycol.

[13] Grummer, R.R., R. D. Shaver, and S. Gunderson. "Feed Additives for the Transition Cow." University of Wisconsin. http://www.wisc.edu/dysci/uwex/nutritn/pubs/NutrAndMgt/tristate901.pdf

---

FEDERAL ORGANIC FOODS PRODUCTION ACT OF 1990

6509 ANIMAL PRODUCTION PRACTICES AND MATERIALS.

(a) **In General**. Any livestock that is to be slaughtered and sold or labeled as organically produced shall be raised in accordance with this chapter.

(d) **Health Care**.

1) **Prohibited Practices**. For a farm to be certified under this chapter as an organic farm with respect to the livestock produced by such farm, producers on such farm shall not

(A) use subtherapeutic doses of antibiotics;

(B) use synthetic internal parasiticides on a routine basis; or

(C) administer medication, other than vaccinations, in the absence of illness.

2) **Standards**. The National Organic Standards Board shall recommend to the Secretary standards in addition to those in paragraph (1) for the care of livestock to ensure that such livestock is organically produced.

(e) **Additional Guidelines**.

2) **Dairy Livestock** A dairy animal from which milk or milk products will be sold or labeled as organically produced shall be raised and handled in accordance with this chapter for not less than the 12-month period immediately prior to the sale of such milk and milk products.

6517 NATIONAL LIST.

(c) **Guidelines for Prohibitions or Exemptions**.

1) **Exemption for Prohibited Substances**. The National List may provide for the use of substances in an organic farming or handling operation that are otherwise prohibited under this chapter only if

(A) the Secretary determines, in consultation with the Secretary of Health and Human Services and the Administrator of the Environmental Protection Agency, that the use of such substances

(i) would not be harmful to human health or the environment;

(ii) is necessary to the production or handling of the agricultural product because of unavailability of wholly natural substitute products; and

(iii) is consistent with organic farming and handling;

(B) the substance

(i) is used in production and contains an active synthetic ingredient in the following categories: copper and sulfur compounds; toxins derived from bacteria; pheromones, soaps, horticultural oils, fish emulsions, treated seed, vitamins and minerals; livestock paraciticides and medicines and production aids including netting, tree wraps and seals, insect traps, sticky barriers, row covers, and equipment cleansers;

(ii) is used in production and contains synthetic inert ingredients that are not classified by the Administrator of the Environmental Protection Agency as inerts of toxicological concern; or

(iii) is used in handling and is non-synthetic but is not organically produced; and

(C) the specific exemption is developed using the procedures described in subsection (d) of this section.[14]

CODE OF FEDERAL REGULATIONS
Title 21, Volume 3
Revised as of April 1, 2001

21CFR184.1666

TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

PART 184--DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE

Subpart B--Listing of Specific Substances Affirmed as GRAS

Sec. 184.**1666** Propylene glycol.

(a) Propylene glycol (C3H8O2, CAS Reg. No. 57-55-6) is known as 1,2-propanediol. It does not occur in nature. Propylene glycol is manufactured by treating propylene with chlorinated water to form the chlorohydrin which is converted to the glycol by treatment with sodium carbonate solution. It is also prepared by heating glyercol with sodium hydroxide.

(b) The ingredient meets the specifications of the Food Chemicals Codex, 3d Ed. (1981), p. 255, which is incorporated by reference. Copies may be obtained from the National Academy Press, 2101 Constitution Ave. NW., Washington, DC 20418. It is also available for inspection at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC 20408.

(c) The ingredient is used as an anticaking agent as defined in Sec. 170.3(o)(1) of this chapter; antioxidant as defined in Sec. 170.3(o)(3) of this chapter; dough strengthener as defined in Sec. 170.3(o)(6) of this chapter; emulsifier as defined in Sec. 170.3(o)(8) of this chapter; flavor agent as defined in Sec. 170.3(o)(12) of this chapter; formulation aid as defined in Sec. 170.3(o)(14) of this chapter; humectant as defined in Sec. 170.3(o)(16) of this chapter; processing aid as defined in Sec. 170.3(o)(24) of this chapter; solvent and vehicle as defined in Sec. 170.3(o)(27) of this chapter; stabilizer and thickener as defined in Sec. 170.3(o)(28) of this chapter; surface-active agent as defined in Sec. 170.3(o)(29) of this chapter; and texturizer as defined in Sec.170.3(o)(32) of this chapter.

[14] Federal Organic Foods Production Act of 1990. U.S. Food and Drug Administration. http://www.ams.usda.gov/nop/orgact.htm

(d) The ingredient is used in foods at levels not to exceed current good manufacturing practice in accordance with Sec. 184.1(b)(1). Current good manufacturing practice results in maximum levels, as served, of 5 percent for alcoholic beverages, as defined in Sec. 170.3(n)(2) of this chapter; 24 percent for confections and frostings as defined in Sec. 170.3(n)(9) of this chapter; 2.5 percent for frozen dairy products as defined in Sec. 170.3(n)(20) of this chapter; 97 percent for seasonings and flavorings as defined in Sec. 170.3(n)(26) of this chapter; 5 percent for nuts and nut products as defined in Sec. 170.3(n)(32) of this chapter; and 2.0 percent for all other food categories.

(e) Prior sanctions for this ingredient different from the uses established in this section do not exist or have been waived.

[47 FR 27812, June 25, 1982][15]

CODE OF FEDERAL REGULATIONS
Title 21 - Food and Drugs
Revised as of April 1, 2001

21CFR589.1001

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

PART 589--SUBSTANCES PROHIBITED FROM USE IN ANIMAL FOOD OR FEED

Subpart B--Listing of Specific Substances Prohibited From Use in Animal Food or Feed

Sec. 589.**1001** Propylene glycol in or on cat food.

The Food and Drug Administration has determined that propylene glycol in or on cat food has not been shown by adequate scientific data to be safe for use. Use of propylene glycol in or on cat food causes the feed to be adulterated and in violation of the Federal Food, Drug, and Cosmetic Act (the act), in the absence of a regulation providing for its safe use as a food additive under section 409 of the act, unless it is subject to an effective notice of claimed investigational exemption for a food additive under Sec. 570.17 of this chapter, or unless the substance is intended for use as a new animal drug and is subject to an approved application under section 512 of the act or an effective notice of claimed investigational exemption for a new animal drug under part 511 of this chapter.

[61 FR 19544, May 2, 1996][16]

NOP:

NATIONAL ORGANIC PROGRAM
Organic Production and Handling
December 2000

[15] 21CFR184.1666, Code of Federal Regulations. U.S. Food and Drug Administration. Revised 1 April 2001. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/ShowCFR.cfm?FR=184.1666

[16] 21CFR589.1001, Code of Federal Regulations. U.S. Food and Drug Administration. Revised 1 April 2001. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/showCFR.cfm?CFRPart=589&showFR=1

Livestock Standards:
These standards apply to animals used for meat, milk, eggs, and other animal products represented as organically produced. Animals for slaughter must be raised under organic management from the last third of gestation, or no later than the second day of life for poultry. Producers are required to feed livestock agricultural feed products that are 100 percent organic, but may also provide allowed vitamin and mineral supplements. Producers may convert an entire, distinct dairy herd to organic production by providing 80 percent organically produced feed for 9 months, followed by 3 months of 100 percent organically produced feed. Organically raised animals may not be given hormones to promote growth, or antibiotics for any reason. Preventive management practices, including the use of vaccines, will be used to keep animals healthy. Producers are prohibited from withholding treatment from a sick or injured animal; however, animals treated with a prohibited medication may not be sold as organic. All organically raised animals must have access to the outdoors, including access to pasture for ruminants. They may be temporarily confined only for reasons of health, safety, the animal's stage of production, or to protect soil or water quality.

All non-agricultural ingredients, whether synthetic or non-synthetic, must be included on the National List of Allowed Synthetic and Prohibited Non-Synthetic Substances. Handlers must prevent the commingling of organic with non-organic products and protect organic products from contact with prohibited substances. In a processed product labeled as "organic," all agricultural ingredients must be organically produced, unless the ingredient(s) is not commercially available in organic form." [17]

NOSB: The National Organic Standards Board (NOSB) makes no mention of propylene glycol in animal production, but does appear opposed to its use in organic crop farming in a recommendation to the USDA in 1998. Excerpt below.

National Organic Standards Board
Ontario, CA
March 16-20, 1998

PROCESSING, HANDLING, AND LABELING COMMITTEE REPORT AND ADOPTED RECOMMENDATIONS TO THE SECRETARY

II. Areas in Proposed Rule that need modification and/or clarification from USDA

§205.16 (a)(2)(iii) Product Composition
"A non-organically produced agricultural product or a non-agricultural ingredient included on the National List that is extracted without the use of a synthetic volatile solvent or which does not contain propylene glycol as a carrier, if commercially available, shall be selected in preference to a product or ingredient that is extracted with a synthetic volatile solvent or which contains propylene glycol as a carrier."

*Committee recommendation: Delete. Organically produced alternatives which do not use propylene glycol or hexane extracted solvents are commercially available. Follow NOSB recommendations concerning the use of natural flavors and oil extraction which do not allow propylene glycol or hexane extraction.[18]

---

[17] "Organic Production and Handling Standards." National Organic Program. December 2000. http://www.ams.usda.gov/nop/facts/standards.htm

[18] "Processing, Handling, and Labeling Committee Report and Adopted Recommendations to the Secretary." National Organic Standards Board. March 16-20, 1998. http://www.ams.usda.gov/nop/NOSB%20Pages%20&%20Files/NOSB%20Recommendation%20Files/NOSB%20Proposed%20Rule%20Comments/process_mod.txt

Regulatory: EPA/Other Sources:

OSHA: None

ACGIH: None

NIOSH: Criteria Document: None

CERHR: The CERHR plans to hold an expert panel evaluation of ethylene glycol (CASRN:107-21-1) and propylene glycol (CASRN: 57-55-6). The exact date for this expert panel meeting is not yet set, but is tentatively planned for the fall of 2002. [Announced February 8, 2002.]

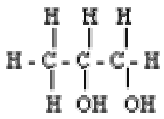
EPA: I.B. Reference Concentration for Chronic Inhalation Exposure (RfC):

"The health effects data for propylene glycol were reviewed by the U.S. EPA RfD/RfC Work Group and determined to be inadequate for the derivation of an inhalation RfC. The verification status of this chemical is currently not verifiable. For additional information on the health effects of this chemical, interested parties are referred to the EPA documentation listed at the website. This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential."[19]

NIEHS/NTP:

Propylene Glycol (CAS No. 57-55-6): Reproduction and Fertility Assessment in CD-1 Mice When Administered in Drinking Water

Structure:



NTP Report # RACB84068

Abstract

Propylene glycol, a common solvent used in industry, food, and in consumer goods, was tested for reproductive toxicity in Swiss CD-1 mice using the RACB protocol. It was part of a series of glycol ethers and congeners evaluated for structure-activity correlations using this design. Data collected on body weights, clinical signs, and food/water consumption during the dose-range-finding segment (Task 1) were used to set concentrations for the main study (Task 2) at 0.0, 1.0, 2.5, 5.0% PG in drinking water. These concentrations produced calculated consumption estimates of nearly equal to 1.819, 4.796, and 10.118 g/kg body weight/d.

Although water consumption in the F_0 generation was consistently higher for all groups (by 6 to 15%), these increases were not statistically different from controls. There was no effect on body weights during either the continuous cohabitation portion of the study. All groups had greater than or equal to 4.6 litters/pair, with greater than or equal to 11.9 pups/litter. There was no treatment-related effect on pup weight adjusted for litter size (control value: 1.55 g). The viability and growth of the final litter was unaffected by PG consumption.

[19] "Health and Environmental Effects Document for Propylene Glycol." U.S. EPA. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington DC. 1987.
http://www.epa.gov/iris/subst/0543.htm#carc

Since there was no effect on fertility, a Task 3 crossover was not conducted. At the time this study was conducted, the protocol called for no necropsy of F_0 animals in the absence of a fertility effect, so the F_0 mice were killed and discarded without necropsy.

For the second generation, just the control and 5% PG groups were evaluated. There was no treatment-related effect on mating, fertility, or on the number, weight, or viability of the F_2 offspring.

After delivery of the F_2 pups, the F_1 adults were killed and necropsied. There was no effect on body or organ weights in males or females, no change in sperm endpoints, and no change in estrous cycle parameters. Serum total calcium levels were measured in serum of the F_1 mice, and was found unchanged by PG exposure from a control value of 9.2 mg/dL.

In summary, propylene glycol, under the conditions of this experiment, has no effect on fertility and reproduction in either generation of Swiss mice at up to 10 g/kg/day.

Report Date: September 1985 [20]

Status Among U.S. Certifiers

State Organic Certifiers:
Minnesota: Follows USDA suggested guidelines.
Ohio: Propylene glycol may not be used in organic crops, livestock, or processing, since it is not specifically mentioned in the National List as an allowable synthetic substance.[21]
Oregon: Follows USDA suggested guidelines.
Pennsylvania: Follows OMRI suggested guidelines.

International

IFOAM: In the 2000 final rule[22] and in the 2002 final draft, there is no specific mention of propylene glycol as permissible. Pertinent excerpts regarding the use of veterinary medicines in organic production follow.

INTERNATIONAL FEDERATION OF ORGANIC AGRICULTURE MOVEMENTS
Basic Standards for Organic Production and Processing
Final Draft 2002

To be voted on at the general assembly
Victoria, August 26-28, 2002

[20] "Propylene Glycol (CAS No. 57-55-6): Reproduction and Fertility Assessment in CD-1 Mice When Administered in Drinking Water." National Toxicology Program. 1985. http://ntp-server.niehs.nih.gov/htdocs/RT-studies/RACB84068.html
[21] Sears, Steve. Administrator, Ohio Ecological Farm and Food Association. Telephone interview, 5 June 2002.
[22] "IFOAM Basic Standards for Organic Production and Processing, Final 2000." International Federation of Organic Agriculture Movements. http://www.ifoam.org/standard/basics.html

5.7. Veterinary Medicine

General Principle

Organic management practices promote and maintain the health and well-being of animals through balanced organic nutrition, stress-free living conditions and breed selection for resistance to diseases, parasites and infections.

Recommendations

Operators should maintain animal health and practice disease prevention through the following techniques:

- Selection of appropriate breeds or strains of animals
- Adoption of animal husbandry practices appropriate to the requirements of each species, such as regular exercise and access to pasture and/or open-air runs, to encourage the natural immunological defence of animal to stimulate natural immunity and tolerance to diseases
- Provision of good quality organic feed
- Appropriate stocking densities
- Grazing rotation and management

Operators should use natural medicines and treatments, including homeopathy, ayurvedic medicine and acupuncture whenever appropriate.

When illness does occur an operator should determine the cause and prevent future outbreaks by adopting appropriate management practices.

Standards shall require that:

5.7.1.
The operator shall take all practical measures to ensure the health and well-being of the animals through preventative animal husbandry practices.

5.7.2.
If an animal becomes sick or injured despite preventative measures that animal shall be treated promptly and adequately, if necessary in isolation and in suitable housing. Producers shall not withhold medication where it will result in unnecessary suffering of the livestock, even if the use of such medication will cause the animal to lose its organic status.

An operator may use chemical allopathic veterinary drugs or antibiotics only if:
- preventive and alternative practises are unlikely to be effective to cure sickness or injury
- they are used under the supervision of a veterinarian, and
- withholding periods shall be not less than double of that required by legislation, or a minimum of 48 hours, whichever is longer.

5.7.3.
Substances of synthetic origin used to stimulate production or suppress natural growth are prohibited

5.7.4.
Vaccinations are allowed with the following limitations:
- when an endemic disease is known or expected to be a problem in the region of the farm and where this diseases cannot be controlled by other management techniques; or
- when a vaccination is legally required, and
- the vaccine is not genetically engineered. [23]

[23] "IFOAM Basic Standards for Organic Production and Processing: Final Draft 2002." International Federation of Organic Agriculture Movements. http://www.ifoam.org/standard/ibs_final02.html

---

Canadian General Standards:
Propylene glycol is not listed on the list of approved livestock materials. The following concerns veterinary medicines as used in organic livestock production.

National Standard of Canada
Organic Agriculture
June 1999

7. **LIVESTOCK PRODUCTION**

7.2 **Feed**

7.2.3 The following products shall under no circumstances be included or added to a livestock animal's diet: feed medications, including all hormones and antibiotics used to promote growth, synthetic appetence modifiers, preservation agents (subject to par. 7.2.5), colouring agents, urea, animal by-products (slaughterhouse waste), dung, droppings or other animal waste, medicated feeds, genetically engineered and/or modified organisms (GEO/GMO) or their products, feeds that have been defattened using solvents (hexane, etc.), chemically-extracted feeds (soy-canola or other meals) or feeds to which other chemicals or prohibited substances have been added.

7.4 **Health**

7.4.1 In cases where disease and health problems require treatment, the use of biological, cultural and physical treatments and/or practices are recommended. If no alternative treatment or management practice exists, substances for veterinary use, as described in A ppendix B, section B2, are permitted. If a veterinary drug treatment is used the withdrawal period shall be at least double the permitted federal withdrawal period allowed for veterinary drugs. The withholding of necessary veterinary treatments in order to maintain the organic status of the affected animal is not permitted.

7.4.2 Vaccination of livestock and therapeutic use of veterinary drugs are permitted only when it has been documented that the targeted diseases are communicable to livestock on the enterprise and cannot be combated by other means.

7.4.3 Allopathic treatments (see Appendix B, section B2), shall be used only as a last resort and are to be aimed at preventing the needless suffering of livestock. If an allopathic treatment is used, the withdrawal period shall be at least double the permitted federal withdrawal period allowed for veterinary drugs.

7.4.4 No products from livestock treated with synthetic antibiotics, parasitides, or other synthetic veterinary compounds not permitted in this standard, with the exception of vaccines, shall be labeled or marketed as certified organic, in accordance with this standard, until an interval of time that is at least double the permitted federal withdrawal period allowed for such veterinary compounds has been exceeded for the treated animal.

7.4.5 All treatments of diseased livestock shall be recorded and individual animals clearly identified. This record shall contain details concerning all treatments, including, but not limited to, the duration of treatment and trade names of the drugs used. Records of all treatments should be kept along with adequate animal/flock/colony identification at all stages of production, transportation, distribution, slaughter, and processing. The operator shall record the method of disposal of milk, waste, or other products from treated livestock. Shipping of diseased livestock to slaughter for human consumption is not permitted.

7.4.6 The use of any synthetic compound to stimulate or retard growth and/or production is prohibited (see Appendix B, section B2). [24]

The **Certified Organic Associations of British Columbia (COABC)** mentions propylene glycol in its restrictions on the labeling of natural flavors as organic. In Section 9.14 of the British Columbia Certified Organic Production Policies and Farm Management Standards, COABC states:

"Allowed as WOI (With Organic Ingredients) (only in products made with organic ingredients). Natural flavors used in products that are made with organic ingredients (WOI) may not contain propylene glycol or any artificial preservatives, and may not be hexane extracted."[25]

EEC/UK:

In general, "propylene glycol" is permitted in the EU as a veterinary medicine in food animals (Annex II; Regulation amending Annex of Regulation 2377/90: Reg. 270/97) [26]

The following guidelines are with regard to veterinary treatment of organic livestock in the EU. There is no specific mention or approval of propylene glycol in this document. An addition in the UK version of organic standards calls for an "allow[ance] for the evolution of a farming system progressively less dependent on allopathic veterinary medicinal products." [27]

ANNEXES I-VIII TO COUNCIL REGULATION (EEC) No. 2092/91
June 24, 1991

5. **Disease prevention and veterinary treatment**

5.1. Disease prevention in organic livestock production shall be based on the following principles:

(a) the selection of appropriate breeds or strains of animals as detailed in Section 3;

(b) the application of animal husbandry practices appropriate to the requirements of each species, encouraging strong resistance to disease and the prevention of infections;

(c) the use of high quality feed, together, with regular exercise and access to pasturage, having the effect of encouraging the natural immunological defence of the animal;

(d) ensuring an appropriate density of livestock, thus avoiding overstocking and any resulting animal health problems.

---

[24] "National Standard for Organic Agriculture." Canadian General Standards Board Sales Centre Public Works and Government Services Canada, Hull, Quebec, K1A 1G6. June 1999.
[25] Section 9.14, British Columbia Certified Organic Production Policies and Farm Management Standards. Certified Organic Associations of British Columbia. http://www.certifiedorganic.bc.ca/standards/section9.14.htm
[26] "Status of MRL Procedures: MRL assessments in the context of Council Regulation (EEC) 2377/90." European Agency for the Evaluation of Medicinal Products. 12 July 2002. http://www.emea.eu.int/pdfs/vet/srwp/076599en.pdf
[27] "Standards for Organic Food Production." UK Register of Organic Foods Standards. February/November 2001. http://www.defra.gov.uk/farm/organic/ukrofs/standard.pdf

5.2. The principles set out above, should limit animal-health problems so that they can be controlled mainly by prevention.

5.3. If, despite all of the above preventive measures, an animal becomes sick or injured, it must be treated immediately, if necessary in isolation, and in suitable housing.

5.4. The use of veterinary medicinal products in organic farming shall comply with the following principles:

(a) Phytotherapeutic (e.g. plant extracts (excluding antibiotics), essences, etc.), homeopathic products (e.g. plant, animal or mineral substances) and trace elements and products listed in Part C, section 3 of Annex II, shall be used in preference to chemically-synthesised allopathic veterinary medicinal products or antibiotics, provided that their therapeutic effect is effective for the species of animal, and the condition for which the treatment is intended;

(b) If the use of the above products should not prove, or is unlikely to be, effective in combating illness or injury, and treatment is essential to avoid suffering or distress to the animal, chemically-synthesised allopathic veterinary medicinal products or antibiotics may be used under the responsibility of a veterinarian;

(c) The use of chemically synthesised allopathic veterinary medicinal products or antibiotics for preventive treatments is prohibited;

5.5. In addition to the above principles, the following rules shall apply:

(a) the use of substances to promote growth or production, (including antibiotics, coccidiostatics and other artificial aids for growth promotion purposes) and the use of hormones or similar substances to control reproduction (e.g. induction or synchronisation of oestrus), or for other purposes, is prohibited. Nevertheless, hormones may be administered to an individual animal, as a form of therapeutic veterinary treatment;

(b) veterinary treatments to animals, or treatments to buildings, equipment and facilities, which are compulsory under national or Community legislation shall be authorised, including the use of immunological veterinary medicinal products when a disease has been recognised as present in a specific area in which the production unit is located.

5.6. Whenever veterinary medicinal products are to be used the type of product must be recorded clearly, (including an indication of the active pharmacological substances involved) together with details of the diagnosis; the posology; the method of administration; the duration of the treatment, and the legal withdrawal period. This information is to be declared to the inspection authority or body before the livestock or livestock products are marketed as organically produced. Livestock treated must be clearly identified, individually in the case of large animals; individually or by batch, in the case of poultry and small animals.

5.7. The withdrawal period between the last administration of an allopathic veterinary medicinal product to an animal under normal conditions of use, and the production of organically produced foodstuffs from such animals, is to be twice the legal withdrawal period or, in a case in which this period is not specified, 48 hours.

5.8. With the exception of vaccinations, treatments for parasites and any compulsory eradication schemes established by Member States, where an animal or group of animals receive more than two or a maximum of three courses of treatments with chemically-synthesised allopathic veterinary medicinal products or antibiotics within one year (or more than one course of treatment if their productive lifecycle is less than one year) the lifestock concerned, or produce derived from them, may not be sold as being products produced in accordance with this Regulation, and the livestock must undergo the conversion periods laid down in Section 2 of this Annex, subject to the agreement of the inspection authority or body.[28]

[28] "Annexes I-VIII to Council Regulation (EEC) No 2092/91 of 24 June 1991." European Union. February 2002. http://www.defra.gov.uk/farm/organic/reg2092annex.pdf

---

Japan Agricultural Standards for Organic Agricultural Products and Their Processed Foods:
Propylene glycol not mentioned. [29]

Section 2119 OFPA U.S.C. 6518(m)(1-7) Criteria

1. *The potential of the substance for detrimental interactions with other materials used in organic farming systems.*

The intended use of propylene glycol as a drench treatment would not result in direct interaction with other materials used in organic farming systems. There is no indication of detrimental interactions from this application.

2. *The toxicity and mode of action of the substance and of its break down products or any contaminants, and their persistence and areas of concentration in the environment.*

a. Toxicity:
Propylene glycol is currently on the FDA's GRAS list, with the exception of when it is used in or on cat food. It is "practically nontoxic," with the probable oral lethal dose in humans above 15g/kg; for a 70 kg person (150 lbs.), more than 1 quart (2.2 lbs.).

Mallinckrodt Chemicals provides the following information and laboratory test results:

Potential Health Effects:
Inhalation: No adverse health effects via inhalation.
Ingestion: Relatively non-toxic. Ingestion of sizable amount (over 100ml) may cause some gastrointestinal upset and temporary central nervous system depression. Effects appear more severe in individuals with kidney problems.
Skin Contact: Mild irritant and defatting agent, especially on prolonged contact.
Eye Contact: May cause transitory stinging and tearing.
Chronic Exposure: Lactic acidosis, stupor, and seizures have been reported following chronic ingestion.
Aggravation of Pre-existing Conditions: Kidney disorders

Oral rat LD50: 20g/kg. Skin rabbit LD50: 20.8g/kg.
Irritation: Eye rabbit/Draize, 500 mg/24H mild.
Investigated as a mutagen and reproductive effector. [30]

\Cancer Lists\

Ingredient	---NTP Carcinogen--- Known	Anticipated	IARC Category
Propylene Glycol (57-55-6)	No	No	None

Arco Chemical Company's MSDS states:

> "Overexposure to this material (or its components) has apparently been found to cause the following effects in laboratory animals: liver abnormalities, kidney damage."

[29] Japanese Agricultural Standards. http://www.fas.usda.gov/gainfiles/200004/25647377.pdf
[30] "Material Safety Data Sheet: Propylene Glycol." Mallinckrodt Chemicals. http://www.mallchem.com/msds/p6928.htm 2 November 2001.

It quotes a review by the American Academy of Dermatologists Inc. [January 1991], which stated that propylene glycol causes a significant number of reactions and was a primary irritant to the skin even in low concentrations.

> "It has been shown that propylene glycol:
> - has severe adverse health effects and has been found to cause contact dermatitis, kidney damage, and liver abnormalities
> - inhibits skin growth in human tests
> - damages cell membranes causing skin rashes, dry skin, and surface damage."[31]

However, contradictory evidence is presented by the following study:

"Propylene glycol generally produces no significant irritant action upon the skin. From the results of extensive studies ... on some 866 human subjects with various dermatologic backgrounds, it appears that propylene glycol may cause primary skin irritation in some people, possibly due to dehydration, but the material does not appear to be a sensitizer. Because of the very low systemic toxicity of propylene glycol, no problem from percutaneous absorption can be anticipated."[32]

In other experiments, propylene glycol has been found to have no effect on fertility and reproduction in generations of Swiss mice at up to 10 g/kg/day.[33] (See NIEHS/NTP report, p. 11) However, propylene glycol can cause temporary grogginess and nausea.[34]

b. Ecological Impact:
When released into the soil, this material is expected to readily biodegrade. When released into the soil, this material is expected to leach into groundwater. When released into water, this material is expected to readily biodegrade. When released into the air, this material is expected to be readily degraded by reaction with photochemically produced hydroxyl radicals. When released into the air, this material is expected to have a half-life between 1 and 10 days.[35]

Intermediates formed during the anaerobic decomposition of propylene glycol under methanogenic conditions have been studied using a serum bottle technique. The pathway is similar to the anaerobic decomposition of ethylene glycol as previously reported. The decomposition is believed to proceed via an initial disproportionation of the glycol to form equal molar amounts of the volatile fatty acid and normal alcohol of the same chain length. The disproportionation of propylene glycol produces propionate and n-propanol. Following disproportionation, the alcohols produced from glycol fermentation are oxidized to their corresponding volatile fatty acids with the reduction of protons to form hydrogen. Ethanol and propionate oxidation to acetate proceeds via a well-established syntrophic pathway that is favorable only under low hydrogen partial pressures. Subsequent degradation of acetate proceeds via acetoclastic methanogenesis with the production of carbon dioxide and methane. Despite the production of hydrogen in the initial steps of glycol degradation, both compounds are completely degradable under the methanogenic conditions tested in studies.[36]

3. *The probability of environmental contamination during manufacture, use, misuse, or disposal of the substance.*

---

[31] "Material Safety Data Sheet: Propylene Glycol." Arco Chemical Company. http://www.rimart.com/harmtech/0475.pdf
[32] Clayton, G. D. and F. E. Clayton (eds.). *Patty's Industrial Hygiene and Toxicology*: Volume 2A, 2B, 2C: Toxicology. 3rd ed. New York: John Wiley Sons, 1981-1982. pp. 3857.
[33] "NTIS# PB86140662." National Technical Information Service. http://www.ntis.gov September 1985.
[34] *Environmental Health Perspectives*. vol. 103, no. 4. April 1995
[35] "Material Safety Data Sheet: Propylene Glycol." Mallinckrodt Chemicals. http://www.mallchem.com/msds/p6928.htm 2 November 2001.
[36] Veltman, S, Schoenberg, T, and Switzenbaum, MS. "Alcohol and acid formation during the anaerobic decomposition of propylene glycol under methanogenic conditions." *Biodegradation*, vol. 9, no. 2. 1998. pp. 113-118.

Manufacturing propylene glycol from propylene, a petrochemical feedstock, presents environmental concerns. Propylene glycol itself does not appear to pose concerns.

Disposal Considerations: Whatever cannot be saved for recovery or recycling should be managed in an appropriate and approved waste disposal facility. Processing, use or contamination of this product may change the waste management options. State and local disposal regulations may differ from federal disposal regulations. Dispose of container and unused contents in accordance with federal, state and local requirements.

Transport Information: Propylene glycol is not regulated by the U.S. Department of Transportation.

4. *The effects of the substance on human health.*
(Please see item 2, Toxicity.)

One previously unanticipated cause of toxic levels of propylene glycol in the body, in which adverse effects have been documented, is in the case of some patients using the drug AGENERASE ® (agenavir) Oral Solution. Agenerase is a protease inhibitor used in combination with other antiretroviral drugs in the treatment of HIV-1 in patients 4 years of age and older. In May 2000, the FDA issued a warning containing the following:

"Propylene glycol is metabolized by the alcohol and aldehyde dehydrogenase enzyme pathway. This enzyme pathway does not attain full adult activity until 12 to 30 months of age. Some patients (infants and children below the age of 4 years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole) are not able to adequately metabolize and eliminate propylene glycol, thereby leading to its accumulation and potential adverse events. Additionally, other patient subgroups as described below may also be at risk. Although, we have received no reports of death or serious injury that have been attributed to propylene glycol in AGENERASE Oral Solution, there are potential safety concerns regarding AGENERASE Oral Solution due to its high propylene glycol content."[37]

Other human studies involving patients with massive concentrations of propylene glycol in the body are as follows:

"In a patient with renal failure who was unable to excrete propylene glycol in the urine, such retention caused severe central nervous system depression. In addition, lactic acidosis was a prominent feature in this patient; with a large anion gap and a lactic acid level of 80 mEq/l. The patient responded rapidly to intravenous fluids and sodium bicarbonate and on recovery volunteered a history of "gas" exposure. Propylene glycol levels of 70 and 60 mg/dl were found in blood and urine, respectively."[38]

"A 15 month old child had several episodes of hypoglycemia while ingesting 7.5 ml of propylene glycol per day. Seizures developed in an 11 year old boy with multiple endocrine problems and systemic candidiasis who ingested a medication containing propylene glycol."[39]

Evidence shows that the adverse effects are indeed caused by propylene glycol itself, and not its metabolites:

"One-third is excreted via the kidneys as a conjugate with glucuronic acid and the rest is metabolized or excreted in the urine unchanged. This suggests that the organic injury and the central nervous system depressing action is probably due to the excessive presence of the propylene glycol and not to its metabolites or its glucuronide."[40]

---

[37] "Drug Warning: Propylene Glycol in AGENERASE ® Oral Solution." U.S. Food and Drug Administration. May 2000. http://www.fda.gov/medwatch/safety/2000/agener.htm

[38] Haddad, L.M., *Clinical Management of Poisoning and Drug Overdose*. 2nd ed. Philadelphia: W.B. Saunders Co., 1990. pp. 700.

[39] Ellenhorn, M.J. and D.G. Barceloux. *Medical Toxicology - Diagnosis and Treatment of Human Poisoning*. New York: Elsevier Science Publishing Co., Inc., 1988. pp. 810.

[40] Clayton, G. D. and F. E. Clayton (eds.). *Patty's Industrial Hygiene and Toxicology*: Volume 2A, 2B, 2C: Toxicology. 3rd ed. New York: John Wiley Sons, 1981-1982. pp. 3860.

5. *The effects of the substance on biological and chemical interactions in the agroecosystem, including the physiological effects of the substance on soil organisms (including the salt index and solubility of the soil), crops, and livestock.*

When released into the soil, this material is expected to readily biodegrade. When released into the soil, this material is expected to leach into groundwater. When released into water, this material is expected to readily biodegrade. When released into the air, this material is expected to be readily degraded by reaction with photochemically-produced hydroxyl radicals. In air, it is expected to have a half-life between 1 and 10 days. [41]

6. *The alternatives to using the substance in terms of practices or other available materials.*

There is interest within the feed industry in using calcium propionate as a ration additive for transition cows. Research showing ruminal conversion of propylene glycol to propionate suggests the potential for a similar efficacy with calcium propionate. Calcium propionate also enhances bunk stability and may improve intakes where heating of the total mix rations (TMR's) in the feed bunk is a problem.[42]

The following discusses the use of sodium propionate or niacin as ketosis treatments.

Propionate
Similar to PG, propionate is a precursor for glucose synthesis. Sodium propionate fed at the rate of 4 oz per cow per day for the first six weeks of lactation increased glucose and reduced ketone concentrations in blood (Schultz, 1958). There is interest within the feed industry in using calcium propionate as a ration additive for transition cows. Research is needed to evaluate the efficacy of propionate salts in transition diets. Research (Christensen et al., 1997; Grummer et al., 1994) indicating ruminal conversion of PG to propionate suggests the potential for comparable efficacy between PG and propionate salts. Palatability may be a concern with propionate salts when fed at similar rates as PG (Littledike et al., 1981); research is needed. High cost of supplementation likely limits the use of PG and propionate salts to transition diets.

Niacin
Interest with transition cows relates to its role in preventing ketosis and fatty liver, which could be due to reduced fat mobilization or altered glucose metabolism (Drackley, 1993). Although a common additive in transition diets, the evidence for its benefit is equivocal (Skaar et al., 1989). Skaar et al. (1989) found no positive effects of niacin supplementation at 12 grams per day from 17 days prepartum through 105 days postpartum. Niacin supplementation did not influence plasma glucose, NEFA or BHBA or lactation performance. Niacin supplementation tended to increase total liver lipids slightly at calving and at five weeks postpartum. Evidence was cited from the human literature suggesting that niacin may reduce fat export from the liver. Supplementation of 12 grams niacin per day from 19 days prepartum through 36 weeks postpartum did not influence plasma glucose or NEFA or liver triglyceride around parturition or lactation performance (Minor et al., 1998). A summary of 14 treatment comparisons in which niacin was fed (Grummer, unpublished) indicated plasma nonesterified fatty acids were significantly reduced once, increased twice, and not altered 11 times. If restricted to studies in which niacin was fed prepartum or within two weeks postpartum, plasma nonesterified fatty acids were significantly reduced once, increased twice, and not altered 8 times. In 10 comparisons (9 of which niacin treatment began prepartum or prior to two weeks postpartum) plasma ketones were significantly reduced 4 times and not affected 6 times. However, three of the four comparisons in which significant reductions were observed were from a single experiment and corresponded to contrasts between three different doses of niacin to a control treatment (Dufa et al., 1983). [43]

---

[41] "Material Safety Data Sheet: Propylene Glycol." Mallinckrodt Chemicals. http://www.mallchem.com/msds/p6928.htm 2 November 2001.
[42] Department of Animal Sciences, Colorado State University. January 2000.
[43] Grummer, R.R., R. D. Shaver, and S. Gunderson. "Feed Additives for the Transition Cow." University of Wisconsin. http://www.wisc.edu/dysci/uwex/nutritn/pubs/NutrAndMgt/tristate901.pdf

---

7. Its compatibility with a system of sustainable agriculture.

The intended use of propylene glycol as a drench treatment would not result in significant direct interaction with other materials used in organic farming systems. Thus, there is no indication of detrimental interactions in the environment/agroecosystem from this application. However, the manufacture of this synthesized material, when derived from the petrochemical feedstock, raises concerns about environmental effects and toxicity. This method is not compatible with a system of sustainable agriculture. There are ongoing studies regarding alternative methods of producing propylene glycol, for example from glycerol or sugars.

TAP Reviewer Discussion

Reviewer #1*: [Ph.D., PAS. State Extension Dairy Specialist, Central U.S.]*

Observations/OFPA Criteria

As a dairy cattle nutritionist I commonly see and recommend to the use of propylene glycol for the treatment and prevention of ketosis in dairy cattle. From experience and according to the review (FDA GRAS status for everything except cat food) propylene glycol is an extremely safe product for the animal, human, and the environment. Propylene glycol is also readily available to the livestock producer.

There is an alternative treatment for ketosis in the form of I.V. injection of dextrose (glucose), which is allowed and may be necessary in acute (clinical) cased of ketosis where the cow is unable to rise/stand on her own. However, the use of propylene glycol is less invasive to the animal and is safer to use with sub-acute (sub-clinical) ketosis. There is also another treatment available for use as a preventative treatment of ketosis in the form of the feed additive calcium propionate. While these alternative treatments are available I see no reason for this to preclude propylene glycol from being added to the national list for medical use in organic livestock production.

Reviewer 1 Conclusion

While the end products are the same it seems that propylene glycol produced from glycerol (derived from fats or tri-glycerides) would be keeping more in line with organic production philosophies than propylene glycol produced from propylene (a petrochemical by-product). While this difference is noted I can find no reason either in the Federal Organic Foods Production Act of 1990 or the Code of Federal Regulations to impose a restriction on the use of propylene glycol produced by either method.

Reviewer 1 Recommendation Advised to the NOSB

My determination is that propylene glycol is a synthetic compound that should be allowed for use as a drench, gel or feed additive in the prevention and/or treatment of ketosis in ruminants.

Reviewer #2*: [Ph.D. Chair-Food Science and State Extension Specialist, Central U.S.]*

Observations/OFPA Criteria

The Technical Advisory Panel report of propylene glycol, its chemistry and applications is adequate to understand how the compound would be useful in livestock production. As presented, it would appear that propylene glycol would result in little or no harm to most animals (felines being the most notable exception) or the environment. The compound has a long history of use in human foods at relatively high levels (as high as 24% in certain confections) with no evidence of any adverse effects. In the opinion of this reviewer, long term exposure to these high levels of

propylene glycol in the diet has not been adequately evaluated for safety to warrant its use as a general animal food additive.

The role of propylene glycol in the treatment of refractory ketosis is well understood. However, there appear to be a number of alternatives to propylene glycol treatment including proper management of animals pre- and post-parturition as well as glucose and insulin injections.

Propylene glycol, as far as we know, does not occur naturally in measurable quantities, but is produced as a co-product of petrochemical refining. The synthesis of the compound, involving the use of chlorine and other inorganic compounds seems to violate the spirit of the organic legislation and would likely be offensive to many consumers. In its favor, propylene glycol itself does not appear to have adverse environmental impact.

Reviewer 2 Conclusion
Given the data presented in the Technical Advisory Panel report, it seems best to this reviewer to consider propylene glycol to be a synthetic compound.

Reviewer 2 Recommendation Advised to the NOSB
If it is to be allowed at all in animal feeds for organic production, it should be restricted to only those animal exhibiting dangerously acute symptoms of refractory ketosis and specifically excluded from general prophylactic applications.

Reviewer 3 [*Ph.D. Animal Science, M.S. Animal Science. Research and teaching activities related to dairy cattle nutrition and nutrient management on livestock farms. Southeast U.S.]*

Comments on petition

The following information needs to be corrected or added to the petition:

Significant additional data is available in the published literature on the use of propylene glycol to prevent and treat ketosis in lactating cows. More appropriate citations include the following:

- Christensen, J. O., R. R. Grummer, F. E. Rasmusssen and S. J. Bertics. 1997. Effect of method of delivery of propylene glycol on plasma metabolites of feed-restricted cattle. J. Dairy Sci. 80: 563-568.
- Grummer, R. R., J. C. Winkler, S. J. Bertics and V. A. Studer. 1994. Effect of propylene glycol dosage during feed restriction on metabolites in blood of prepartum Holstein heifers. J. Dairy Sci. 77: 3618-3623.
- Johnson, T. R. and D. K. Combs. 1991. Effects of prepartum diet, inert rumen bulk and dietary propylene glycol on dry matter intake of lactating dairy cows. J. Dairy Sci. 74: 933-944.
- Studer, V. A., R. R. Grummer, S. J. Bertics and C. K. Reynolds. 1993. Effect of prepartum propylene glycol administration on periparturient fatty liver in dairy cows. J. Dairy Sci. 76: 2931-2939.
- Effects of propylene glycol drenching on energy balance, plasma glucose, plasma insulin, ovarian function and conception in dairy cows. Anim. Reprod. Sci. 68: 29-43.

OFPA Criteria Evaluation

(1) The potential of such substances for detrimental chemical interactions with other materials used in organic farming systems;

I agree with the criteria evaluation in the petition.

(2) The toxicity and mode of action of the substance and of its breakdown products or any contaminants, and their persistence and areas of concentration in the environment;

I agree with the criteria evaluation.

(3) the probability of environmental contamination during manufacture, use, misuse or disposal of such substance;
I agree with the criteria evaluation.

(4) the effect of the substance on human health;
I agree with the criteria evaluation.

(5) the effects of the substance on biological and chemical interactions in the agroecosystem, including the physiological effects of the substance on soil organisms (including the salt index and solubility of the soil), crops and livestock;
I agree with the criteria evaluation.

(6) the alternatives to using the substance in terms of practices or other available materials; and
I agree with the criteria evaluation, and offer additional supporting information:

Ketosis may be prevented by avoiding overfeeding and overconditioning cows, avoiding abrupt ration changes, and feeding good quality forages. Even with these practices, however, incidence of ketosis averages 12-14% (Doohoo and Martin, 1984; Jorritsma et al., 1998). In addition to propylene glycol and calcium propionate to treat ketosis, intravenous administration of dextrose (Metzner et al., 1993) or dextrose and insulin (Sakai et al., 1993) are used to increase blood sugar levels and treat ketosis. The latter two treatments are not practical as on-farm treatments, however.

Administration of monensin sodium (Rumensin™) has been shown to decrease incidence of ketosis in lactating cows (Sauer et al., 1989, Duffield et al. 1999, Green et al., 1999), but this antibiotic is not approved for use in lactating dairy cows in the United States and would be clearly inappropriate for use on organic farms.

(7) its compatibility with a system of sustainable agriculture.
I agree with the criteria evaluation.

Reviewer 3 Conclusion

Propylene Glycol is a synthetic material due to its production via processing of hydrocarbons. I recommend that it be allowed for use in organic systems with the restrictions on its use. Propylene glycol is an effective treatment for ketosis, a serious health problem in lactating dairy cows affecting 12-14% of the population. It does not have organic substitutes, and its manufacture, use, and disposal do not have adverse effects on the environment. The nutritional quality of food (milk, meat) is maintained when it is used and it does not have adverse effect on human health. It is listed as GRAS by FDA, is not a preservative, and is necessary to the production of organically produced agricultural product as the most effective treatment of a common, serious, health problem in dairy herds.

Reviewer 3 Recommendation Advised to the NOSB

The substance is Synthetic.

For Livestock, the substance should be Added to the National List with restrictions.

I recommend that it be approved as synthetic—allowed with restrictions on its use. The restriction is that the substance should not be used in or on feline diets.

References cited

Dohoo I. R., and S. W. Martin. 1984. Subclinical ketosis: prevalence and associations with production and disease. Can. J. Comp. Med. 48:1-5.

Duffield, T. F., K. E. Leslie, D. Sandals, K. Lissemore, B. W. McBride, J. H. Lumsden, P. Dick, and R. Bagg. 1999. Effect of a Monensin-Controlled Release Capsule on Cow Health and Reproductive Performance. J. Dairy Sci. 82:2377-2384.

Green B. L., B.W. McBride , D. Sandals, K. E. Leslie , R. Bagg, P. Dick. 1999. The impact of a monensin controlled-release capsule on subclinical ketosis in the transition dairy cow. J. Dairy Sci. 82:333-42.

Jorritsma R, S. J. Baldee, Y. H. Schukken, T. Wensing, G. H. Wentink. 1998. Evaluation of a milk test for detection of subclinical ketosis. Vet. Q. 20:108-10.

Metzner M, W. Hofmann, C. Laiblin.1993. The effectiveness of intravenous administration of large quantities of glucose in the treatment of bovine ketosis Tierarztl Prax 21:289-93]

Sakai T, T. Hayakawa, M. Hamakawa, K. Ogura, S. Kubo. 1993. Therapeutic effects of simultaneous use of glucose and insulin in ketotic dairy cows. J Dairy Sci 76:109-14

Sauer, F. D., J. K. G. Kramer and W. J. Cantwell. 1989. Antiketogenic effects of monensin in early lactation. J. Dairy Sci. 72: 436-442.

TAP Conclusion

All three TAP reviewers found propylene glycol to be a synthetic material. Two reviewers support allowance of the substance in livestock with restrictions, while the other supports allowance for all petitioned purposes and without restriction. Concerns included the consistency of the method of manufacturing of propylene glycol with organic practices, and the availability of other methods of treatment and prevention of ketosis.